

MYOCARDIAL INJURY FROM THERAPEUTIC IRRADIATION

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In patients who undergo radiotherapy for malignant disease in the region of the chest, the diagnosis of cardiac infarction has sometimes been entertained when chest pain has appeared as a prominent symptom during or after treatment.

To resolve this diagnosis presupposes a knowledge of the effects of radiation upon the heart, and the changes that such treatment by itself can produce in the electrocardiogram—changes that might resemble those found in cardiac infarction. The present work was undertaken to decide this particular.

THE INVESTIGATION DESCRIBED

Twenty-six patients were assembled for the inquiry. One woman and five men suffered from inoperable carcinoma of the bronchus. Eight women with carcinoma of the right breast and 12 with carcinoma of the left breast had undergone mastectomy. Before radiotherapy, the patients with carcinoma of the bronchus had symptoms attributable to the growth, and none had cardiac pain. Those with carcinoma of the breast were otherwise symptomless.

In all save three patients, clinical, electrocardiographic, and radiological examination showed no abnormal signs in the cardio-arterial system. The three exceptions were Case 3 with systemic hypertension, where the electrocardiogram demonstrated left ventricular preponderance and cardiography showed some enlargement of the left ventricle, and Cases 8 and 12 in which a low and blunt T wave in CR₄ suggested the presence of limited and painless coronary arterial disease.

Irradiation Technique and Dosage. The 6 patients with carcinoma of the bronchus were treated with a radical course of irradiation from a telecobalt 60 unit, and the 20 patients with carcinoma of the breast were given deep X-ray therapy from 250 kilovolt machines directed to the chest wall and the lymphatic drainage areas of the breast. The site of the growth, whether in the bronchus or the breast, determined the place and distribution of the radiotherapy, and the technique differed accordingly in the two groups.

Inoperable Carcinoma of the Bronchus. The neoplasm in each of the six patients was situated medially with a spread into adjacent mediastinal glands. Radiologically the affected area was limited to 150 sq. cm. Irradiation from a telecobalt 60 unit was applied through two portals of entry, and the total dose received by the growth was 4000 rads which was given in divided doses daily over a period of four weeks.

Carcinoma of the Breast. The chest wall together with the axillary and supraclavicular lymphatic glands of the affected side received a total dose of 3650 roentgens. This was given in divided doses on alternate days over a period of three weeks. The irradiation directed to the axillary and supraclavicular regions did not contribute significantly to the dose received by the heart. The chest wall was treated by three beams of irradiation. The edge of the *medial* applicator was placed on a line drawn from the contralateral sternoclavicular joint vertically down the sternum, and the irradiation

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was directed laterally across the mastectomy scar. The *lateral* applicator was placed parallel to this and along a line proceeding from the mid-axilla. These two applicators were tangential to the curve of the chest so that the irradiation glanced across the chest wall, avoiding as far as possible the underlying lung. The *lower* applicator was arranged at right angles to the lower edges of the other two and was directed upwards across the scar. The total dose of 3650 roentgens was estimated at the central point on the skin between the two parallel applicators. The amount of radiation delivered through each applicator varied in relation to the build of the patient and the distance between the applicators.

The Dose Received by the Heart. Before commencing treatment of each patient with carcinoma of bronchus, a radiograph was taken on the telecobalt 60 unit to ensure that the tumour was in the centre of the beam of irradiation. This radiograph also demonstrated that no critical part of the heart lay within the path of the beam (Fig. 1). Moreover, there was no significant side-scatter from gamma rays.

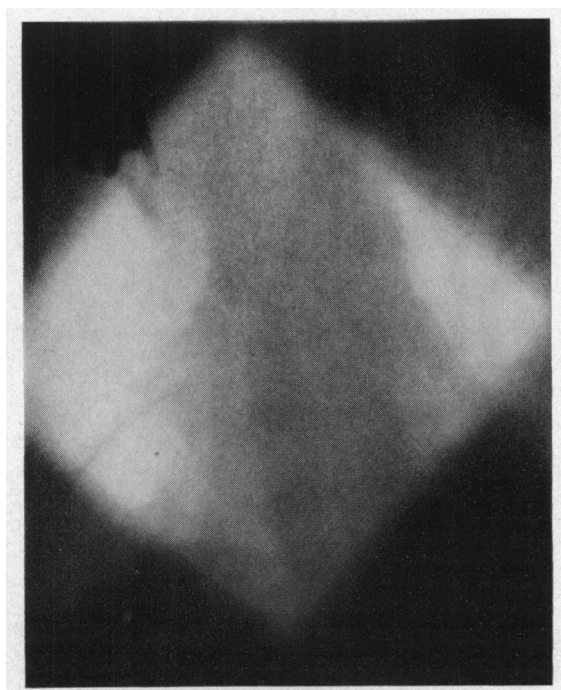


FIG. 1.—Radiograph taken with a telecobalt 60 unit, showing the distribution of the beam of irradiation applied to a carcinoma of the bronchus situated in the region of the carina. No critical portion of the heart lies in the path of the beam.

In patients who had undergone mastectomy for carcinoma of the breast, the position of the heart in relation to the beam of irradiation was determined by means of lead markers. These were attached to the skin over the lines along which the medial and lateral applicators were positioned. The patient was then screened and rotated until both sets of markers came into line when viewed radiologically, and a film was taken.

In patients in whom the right side of the chest was irradiated, no part of the heart shadow appeared inside the boundary delineated by the markers (Fig. 2), but when the left side was so treated a portion of the heart usually extended beyond this demarcation line (Fig. 3).

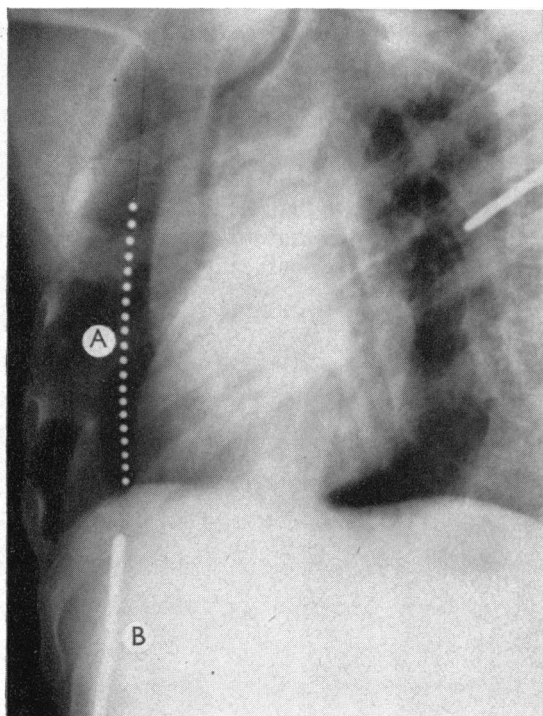


FIG. 2.—The heart shadow in a patient, treated for carcinoma of the right breast, lies wholly behind the lead markers. In that the heart remained outside the beam of irradiation, no changes took place in the electrocardiograms after irradiation. In this and in Fig. 3 and 4, the dotted line (A) marks the site of the medial applicator and the continuous line (B) marks the site of the lateral applicator.

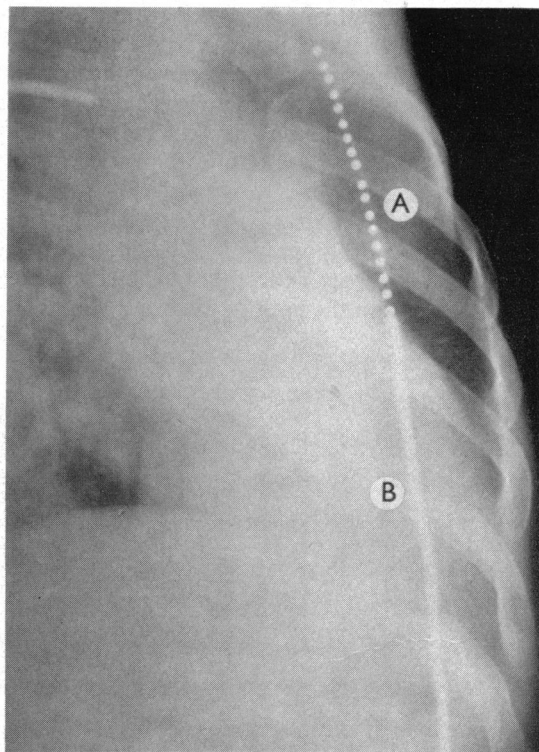


FIG. 3.—A portion of the heart shadow in Case 4, treated for carcinoma of the left breast, lies in front of the lead markers. In that it intercepted the beam of irradiation, changes took place in the electrocardiogram after irradiation (see Fig. 5).

Careful measurements were then made by means of the isodose curves appropriate to the applicators and the tissues irradiated, and the dose received at three points deep to the skin was calculated. This ranged from 3200 roentgens at the most anterior or superficial point, to 2200 roentgens at the geometrical edge of the beam which was about 6 cm. deep to the skin. Any portion of the heart within the area bounded by the markers received about 3000 roentgens.

Pulmonary Function Tests. These were carried out in each of the six patients suffering from carcinoma of the bronchus, and in twelve with carcinoma of the breast. In four patients in whom electrocardiographic changes followed irradiation, pulmonary function remained normal throughout the period of treatment and at a time when the electrocardiogram was abnormal. These findings do not support the view of Wachtler (1953) that the lung was more sensitive to radiation than the heart, and that lung damage is present in cases where irradiation has injured the heart.

ELECTROCARDIOGRAPHY

An electrocardiogram recorded before radiotherapy had started was a normal tracing except for changes already described in Cases 3, 8, and 12.

Three further electrocardiograms were taken after the completion of treatment. In five patients

(Cases 3, 6, 10, 11, and 12) the first of these was recorded as soon as the period of irradiation had ended. One patient (Case 8) died within two months of the treatment so that only one tracing became available during the post-irradiation period. In the remaining cases four months were allowed to elapse before recording the first post-irradiation electrocardiogram.

CHANGES IN THE ELECTROCARDIOGRAM FOLLOWING IRRADIATION

For the purpose of analysing the changes that took place in the electrocardiogram of the twenty-six patients undergoing radiotherapy, it has been found convenient to discuss them in three groups according to the site irradiated and its relation to the heart.

Irradiation of the Mediastinum. In this group are included the six patients with inoperable carcinoma of the bronchus. In no instance did the post-irradiation electrocardiogram differ from the physiological tracing recorded before the treatment commenced. This caused no surprise in that no critical portion of the heart lay in the path of the beam of irradiation (Fig. 1). One patient died during the period of observation, and shortly before his death a pericardial friction sound was heard. Necropsy showed extensive invasion of the pericardium by the malignant growth. The electrocardiogram in this patient, recorded four months after the conclusion of treatment, and five months before his death, was physiological.

Irradiation of the Right side of the Chest. In this group are included the eight patients with carcinoma of the right breast. In none was the post-irradiation electrocardiogram abnormal, nor was it altered in any particular from the tracing recorded before radiotherapy started.

This finding again caused no surprise in that the path of irradiation did not traverse any part of the heart (Fig. 2).

Irradiation of the Left side of the Chest. In this group are included twelve patients (Cases 1 to 12) in whom mastectomy had been carried out for carcinoma of the left breast. Their ages varied from 36 to 60 years and the average age was 50 years.

In three patients (Cases 9, 10, and 11), the post-irradiation electrocardiogram was unaltered from the pre-irradiation tracing. In each instance a marker film (Fig. 4) showed that the heart lay outside the beam of irradiation. In Case 9 this resulted from a collection of fluid under the scar, while in Cases 10 and 11 the position of the heart in relation to the setting of the applicators was such that no part of the heart remained in the path of the therapeutic beam.

In the remaining nine patients significant electrocardiographic changes had followed radiotherapy. In six (Cases 1, 3, 4, 5, 6, and 12) (Fig. 5 and 6) the changes were obvious, while in three (Cases 2, 7, and 8) (Fig. 7) they were less conspicuous. The cardiographic fault was confined to the T wave and no case showed significant Q waves nor depression of the S-T segment except in Case 3 where this last effect had resulted from hypertension. The T wave in lead I was low or flat in all nine cases, and the wave was also deformed in CR₄, showing frank inversion of the T in six, T-U depression in two, and a cloven T in one.

In every patient with an abnormal electrocardiogram the deformity was present in the tracing recorded four months following radiotherapy. In two of these, when an earlier cardiogram was taken immediately treatment was concluded, changes had not then taken place. The cardiographic deformities discovered four months after treatment were still present in tracings recorded at nine months, but had disappeared from the cardiogram taken twelve months after the conclusion of treatment in each of the five patients followed for that period of time.

THE MEANING OF THE ELECTROCARDIOGRAPHIC CHANGES

It is clear that the cardiographic changes in our cases were not the outcome of a reaction in the pericardium. Thus, in none of the twelve patients submitted to irradiation of the left chest was a pericardial friction sound heard, nor was there any elevation of the "saddle curve" type in the S-T segment in tracings recorded during the immediate post-irradiation period. Moreover, inversion of the T wave disappeared after an interval of 9 to 12 months. In one patient in whom the mediastinum

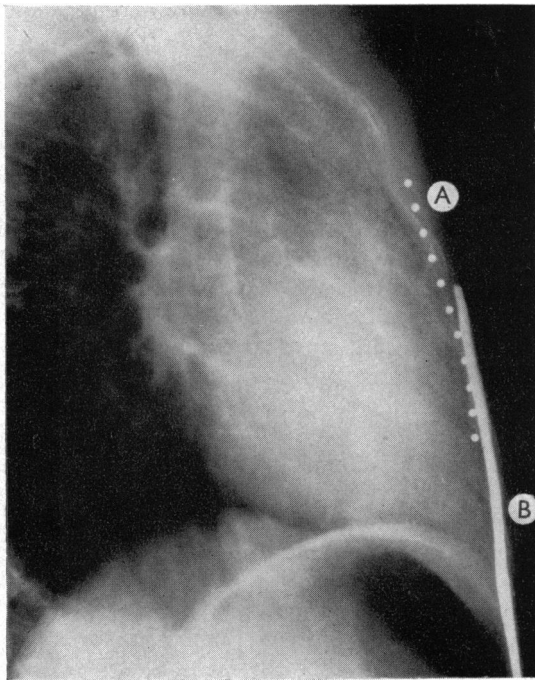


FIG. 4.—The heart shadow in Case 10, treated for carcinoma of the left breast, lies posterior to the lead markers. In that the heart remained outside the beam of irradiation, no changes took place in the post-irradiation electrocardiograms.

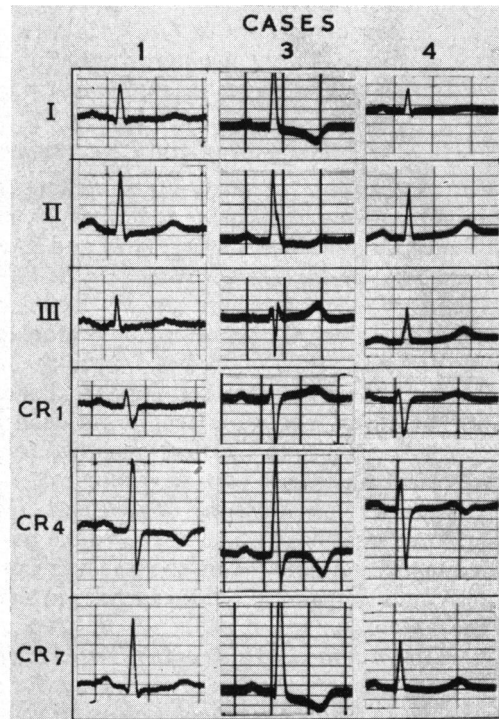


FIG. 5.—Post-irradiation electrocardiogram in three cases treated for carcinoma of the left breast, following mastectomy. The T wave is low in some leads and is inverted in CR4. Changes of left ventricular preponderance from incidental hypertension are added in Case 3.

was irradiated for carcinoma of the bronchus, where the electrocardiogram recorded four months later was a normal tracing, a pericardial friction sound was heard 5 months later, immediately before his death: at necropsy the pericardium was extensively involved by neoplasia. Tricot *et al.* (1954) described a patient who had received five courses of deep X-ray therapy in the treatment of carcinoma of the left breast, the total dosage being 13,000 roentgens: three months before her death she developed a pericardial rub followed by atrial fibrillation and T wave inversion in the electrocardiogram. Necropsy showed constrictive pericarditis in which the pericardium was 4 mm. thick. No such complication has so far happened in our patients, but the dosage in our cases was much less, and so also has been the period of observation. In one of our patients (Case 7) a localized linear deposit of calcium has appeared in the pericardium but her electrocardiogram has fully recovered, and she shows no evidence of constrictive pericarditis.

We have regarded the T wave changes exhibited by our patients as the result of a localized myocardial injury caused by the irradiation, but we have not been afforded the opportunity to examine the lesion histologically in that necropsy was not made available in the single patient (Case 8) who died in the post-irradiation period when the electrocardiogram was abnormal. The limited distribution of the injury is indicated by the absence from all the electrocardiograms of both significant Q waves and depression of the S-T segment. The innocent nature of the lesion is told by the recovery of the tracing to its pre-irradiation state, so that complete resolution of the injured area took place in the absence of fibrotic scarring.

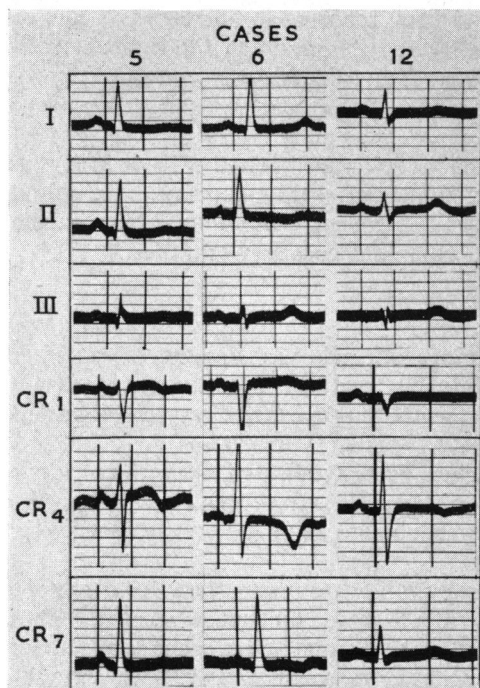


FIG. 6.—Post-irradiation electrocardiogram in three cases treated for carcinoma of the left breast, following mastectomy. The T wave is low in some leads and is inverted in CR₄.

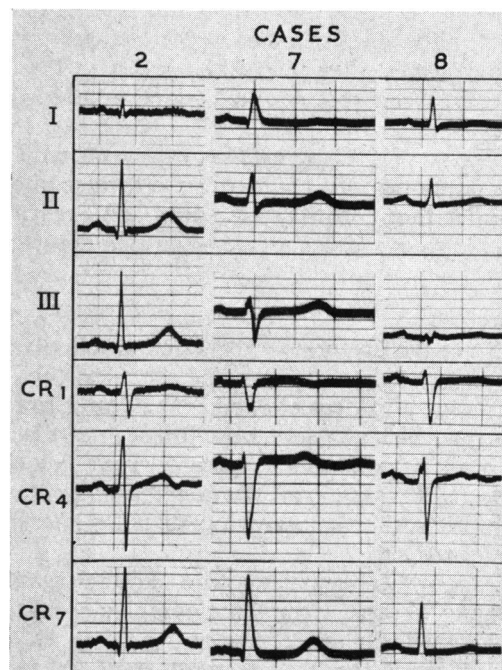


FIG. 7.—Post-irradiation electrocardiogram in three cases treated for carcinoma of the left breast, following mastectomy. The T wave in lead I is low. Depression of T-U segment in CR₄ in Cases 2 and 7, and a cloven T in the same lead in Case 8.

DISCUSSION

In the past the heart has been deliberately exposed to irradiation with the intention of improving myocarditis and aortitis (Beeck and Hirsch, 1916), and endocarditis (Levy and Golden, 1925). Massive experimental irradiation of the thorax, with subsequent histological examination of the heart, has been carried out in dogs and sheep by Hartman *et al.* (1927), and in rats and rabbits by Warthin and Pohle (1929). In both series the injury to the myocardium was considerable, but although such information has value, it would be fallacious to apply to man the results so obtained in animals by means of deliberate heavy irradiation. Thibaudeau and Mattick (1929), however, examined sections taken from the wall of the left ventricle, mid-way between the apex and the mitral valve, and along its lateral border, in 10 cadavers whose hearts in life had been exposed to irradiation in the treatment of adjacent organs affected by malignant disease. This histological examination showed changes that varied from slight interstitial fibrosis to hyaline and fatty degeneration of muscle fibres with necrosis.

Whitfield and Kunkler (1957) have written on the electrocardiographic findings in patients undergoing radiotherapy directed to a carcinoma of the left breast in two patients, to lymphosarcoma of the mediastinum and neck in one patient, and to carcinoma of the bronchus in another. Inversion of the T wave in leads V₁, V₂, and V₃ coincided with the erythematous skin reaction two to five weeks after treatment. Such changes disappeared within two months in three patients, but death ensued unexpectedly in one patient when the treatment had lasted five weeks; histological examination of the heart in this case failed to discover any abnormality. These authors considered that the cardiographic changes had resulted from direct damage to the heart muscle itself and not from

ischæmia secondary to irradiation arterial damage as had been reported in animals as a delayed effect. The electrocardiographic changes in their series located the injury in the right ventricle. In our series, they placed the lesion in the left ventricle. This difference is explained by the different techniques adopted which exposed different portions of the heart to a high dosage of X-rays.

Pearson (1958) reported two patients with left mammary carcinoma treated with deep X-rays, who developed signs of "extensive cardiac infarction" six months after the treatment. He did not consider that coronary atheroma had been the cause, for subsequent clinical and electrocardiographic recovery was greater than that expected from atheromatous coronary occlusion.

SUMMARY AND CONCLUSIONS

Since the diagnosis of cardiac infarction as the source of chest pain has sometimes been entertained in patients in whom the chest has been irradiated during treatment of malignant disease, it is necessary to decide whether incidental irradiation of the heart can cause electrocardiographic changes which simulate those found in cardiac infarction.

In six patients with inoperable carcinoma of the bronchus, and in eight patients with carcinoma of the right breast, in all of whom the path of the therapeutic rays did not traverse any critical portion of the heart, the electrocardiogram taken after irradiation was found to be unaltered from the tracing taken before.

Among twelve patients who had undergone radiotherapy following mastectomy for carcinoma of the left breast, electrocardiographic changes limited to the T waves took place in nine. Thus, the T wave was low or flat in lead I in all nine; in CR₄ the T was cloven once, and showed depression of the T-U segment twice, while in the remaining six patients the T was frankly inverted. This disposition of the deformed T wave placed the injury in the anterior wall of the left ventricle.

The changes appeared within four months of the conclusion of treatment, and rarely earlier than this. They lasted for a period of nine months, and had disappeared completely within twelve months in each of the five patients followed for that period of time. These findings indicate that the myocardial lesion resolved entirely and without scarring, emphasizing the innocent nature of the injury to the heart. This temporary injury seems inevitable when therapeutic irradiation of high dosage is applied in such close proximity to the heart. In three patients in whom irradiation had not affected the electrocardiogram, marker films showed that the heart was so placed in relation to the path of the rays that it lay outside the geometrical edge of the beam.

The importance of the findings lies with the recognition of the cause of the electrocardiographic changes, for should a patient subjected to radiotherapy of the left chest during the previous 12 months, usually in the course of treating carcinoma of the left breast subsequent to mastectomy, suffer from chest pain, changes that may show in the electrocardiogram are more likely to be irradiation effects than those identified with cardiac infarction.

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